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Insulin intensification for people with type 2 diabetes: a practical approach

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REVIEW

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Abstract

Background: Type 2 diabetes is a progressive disorder and with time, it is appropriate for insulin therapy to be initiated in the majority of people. Insulin is commonly initiated with once-daily basal insulin. However, when glycaemic control becomes unsatisfactory despite the introduction of basal insulin, no clear guidelines exist for intensifying the insulin regimen. In this article we aim to provide a clinician's approach to both the optimisation of the basal insulin dose, and strategies to intensify insulin therapy.

Methods: An expert consensus panel, consisting of the authors, was convened to review the current practice of insulin intensification in people with type 2 diabetes and to develop a pragmatic algorithm for clinicians. The panel reviewed the published literature on the use of insulin in clinical practice, the evidence for different intensification strategies, and the potential impact of patient-related factors on insulin choices.

Results: Insulin intensification should only be considered after the basal insulin dose has been optimised. This is achieved by taking into account basal and prandial (pre and post) blood glucose levels, individualised target HbA_{1c}, and dietary factors. If optimal basal insulin together with oral medications is not sufficient to reach glycaemic targets, the next step is to introduce a basal plus 1 regimen or switch to twice-daily premixed insulin. Each has advantages and disadvantages and existing guidelines do not emphasise or support any particular regimen. Therefore, it is important to individualise the choice according to the individual's needs. A practical algorithm has been developed to help clinicians choose an appropriate second-line regimen.

Conclusion: As beta-cell failure progresses in people with type 2 diabetes, basal insulin regimens need to be optimised and then intensified when necessary to maintain agreed glycaemic targets.

Key Words
Diabetes mellitus type 2, insulin therapy.

Background

Type 2 diabetes affects approximately 8% of Australian adults[1] and the prevalence of this condition has at least doubled in the past two decades.[2] It is among the top 10 leading causes of death in both sexes and one of the largest specific contributors to the overall costs of healthcare in Australia.[2] Tight glycaemic control is known to be cost-effective and potentially all people with type 2 diabetes could benefit from effective and individualised glycaemic management.

The management of type 2 diabetes is made more complex by the established progressive nature of the disorder. Thus, while the benefits of achieving and maintaining target glycated haemoglobin (HbA_{1c}) on microvascular complications (neuropathy, nephropathy and retinopathy) have been well documented,[3-6] even on a background of healthy lifestyle, weight control and oral medications (predominantly, metformin and/or sulfonylureas), declining beta cell function often results in the need for insulin in order to maintain a target HbA_{1c}. Indeed, the United Kingdom Prospective Diabetes Study (UKPDS) showed that 53% of people with type 2 diabetes on sulfonylurea monotherapy required insulin therapy after six years. After nine years, this figure increased to 80%.[7]

Basal insulin analogues such as insulin glargine (Lantus®, Sanofi-Aventis); Neutral Protamine Hagedorn (NPH) are widely used as the initial choice of insulin in people with type 2 diabetes whose HbA_{1c} is consistently above 7.0%, despite optimised oral hypoglycaemic agents (OHA). Insulin determir (Levemir®, Novo Nordisk) is also an option for people with type 2 diabetes. Such an insulin approach, often with maintaining OHA therapy, is a recognised best practice option as described in the 2009 National Health and Medical Research Council (NHMRC) Guidelines for Blood Glucose Control in Type 2 Diabetes.[8]

In randomised controlled trials (RCTs) comparing basal analogues (insulin glargine and insulin detemir) with NPH insulin, both agents demonstrated similar reductions in HbA_{1c} and fasting plasma glucose but with lower rates of hypoglycaemia.[9-12] This helps to explain why, in Australia, the use of NPH has declined in favour of basal analogue insulin. Although the efficacy of basal therapy is clear, an increased emphasis on basal initiation rather than optimisation and less emphasis on intensification of insulin therapy (in particular addressing prandial glucose control) has left a significant glycaemic-burden for those already taking insulin. This may be consequent upon an absence of a clear strategy for choosing a second-line insulin regimen. This is particularly relevant for primary care physicians managing insulin therapy and therefore practical advice, based on the available evidence and tailored to the individual is warranted.

In this article, we aim to address the optimisation of the basal insulin dose, and further, to provide a rationalised discussion of the strategies available to intensify insulin therapy when optimised basal insulin no longer achieves glycaemic targets.

METHODS

Sanofi-Aventis convened an expert panel, comprising the authors, to review the management of insulin intensification in people with type 2 diabetes and to discuss the issues faced by clinicians involved in diabetes management. It was considered that a review of insulin intensification was timely given the recent publication of the NHMRC Guidelines.[8] These guidelines outline an accepted approach to diabetes assessment and management and recommend evidence-based targets to decrease the likelihood of microvascular and macrovascular events. While accepting the guidelines as a starting point, our aim was to further emphasise the issues associated with insulin intensification, and more specifically, to:

- Emphasise the importance of optimising basal insulin therapy.
- Review current practice trends and in that context, discuss appropriate thresholds for insulin intensification.
- Review the evidence for different insulin intensification strategies.
- Outline factors to consider when selecting an appropriate insulin intensification regimen.
- Develop a pragmatic algorithm for clinicians.

The expert panel reviewed a large evidence-base related to insulin intensification and identified practical evidence-gaps in the literature. Where possible, consensus informed by evidence was used to guide insulin intensification recommendations. In some situations, the recommendations outlined by the panel were based on collective clinical judgement.

RESULTS

The panel acknowledged the importance of the NHMRC Guidelines[8] and supported the recommendation that while a generic HbA_{1c} target is ≤7.0%, HbA_{1c} targets should be individualised. The benefits of a low-target HbA_{1c} must be balanced against the risk of hypoglycaemia and weight gain, and the potential impact of treatment on quality of life.[13]

Is the basal therapy optimal?

In clinical practice, it is likely that optimisation of basal therapy is significantly delayed, thereby increasing the risk of diabetic complications as control worsens over time. Longitudinal Australian data from Davis et al., suggest that the majority of people with type 2 diabetes spend a considerable time with suboptimal glycaemic control (HbA_{1c} >7.0%), despite the availability of a range of effective therapies.[14] Similarly, several studies have highlighted that target HbA_{1c} goals are, in general, not being achieved in clinical practice globally and in Australia.[15, 16] This observation is supported by data from Brown et al., who calculated the cumulative glycaemic burden (defined as HbA_{1c}-months >8.0% or 7.0%) among 7,208 people receiving treatment with non-drug therapy, sulfonylurea monotherapy, metformin monotherapy, and combination OHA therapy between 1994 and 2002.[17] The average individual accumulated nearly five HbA_{1c}-years of excess glycaemic burden >8.0% from diagnosis until starting insulin and about 10 HbA_{1c}-years of burden >7.0%.

Basal therapy provides a level of background insulinisation to which additional doses of prandial insulin can be added. However, intensification should only occur after the basal insulin dose has been optimised. Optimisation of lifestyle issues (e.g., diet and exercise),

non-adherence with therapy, and the use of other oral medications (particularly metformin) are essential, but for many people, proactive up-titration of the basal insulin dose to achieve agreed pre-prandial (i.e., breakfast and dinner) glucose levels is necessary. If, despite achieving appropriate fasting glucose levels, the HbA_{1c} remains elevated, prandial glycaemic excursions should be assessed by measuring pre- and post-prandial blood glucose. The presence of additional co-morbidities and evidence of organ damage will influence how subsequent titration occurs. Recently, several RCTs have suggested that more intensive therapy is not necessarily associated with improved patient outcomes.[13, 18, 19]

Considering the above, several methods can be used for optimising the basal insulin dose. If the preference is for once-daily basal dosing, insulin glargine would be an appropriate choice, given its longer duration of action, less hypoglycaemia relative to NPH. For some people the maximum capacity of an insulin pen device may limit the capacity to achieve good fasting glucose levels. One option is to dial-in an additional amount of insulin during the same injection. In a small proportion of people, insulin glargine may not provide adequate 24-hour cover,[20] despite the Therapeutic Goods Administration (TGA) authorising insulin glargine for once-daily use. For these individuals, an alternative option is to split the dose into a twice-daily basal regimen.

If target glycaemia is still not achieved, then other factors may need to be considered. Particular individuals may require higher doses of insulin. These include the obese,[21, 22] and those with fatty liver disease.[23]

Intensification of insulin by including prandial cover

Assuming that an optimised basal insulin regimen together with oral medication(s) is not sufficient to achieve prandial glycaemic targets, strategies for insulin intensification may include a switch to premixed insulin (1-3 daily doses),[12, 24-28] a basal plus (+1, +2) regimen,[29-31] or a basal-bolus approach (a basal dose plus injections of a short acting insulin analogue with every meal).[12, 32, 33] The panel considered the next steps after basal insulin therapy and hence focused on the use of a 'basal plus 1' strategy and a 'twice-daily premixed' strategy. Both strategies require two injections per day.

The basal plus 1 regimen involves the addition of a short-acting insulin injection at the time where the post-prandial blood glucose increment is excessive (usually the largest meal of the day).[29] The starting dose of short-acting insulin should be approximately 10% of the basal dose. The dose is then adjusted according to post-prandial blood glucose levels.

When switching from once-daily basal insulin to twice-daily premix, one recommendation is to use approximately the same total basal insulin dose, spilt into equal doses between pre-breakfast and pre-dinner.[34] Another recommendation is that the initial dose should be 80% of the final basal dose with subsequent titration over the following two weeks.[35] An increase in the total daily dose of insulin is likely to be required with this strategy.[25]

Thus, the central question is: which of these strategies – basal plus 1 or twice daily premix, provides the best clinical and practical benefit to people with type 2 diabetes? There is no direct evidence of comparable efficacy for these choices. Importantly the NHMRC Guidelines[8] do not emphasise or support any particular regimen. In general, efficacy increases with the number of injections given and total insulin dose, but so too does the incidence of hypoglycaemic events and weight gain.

Based on clinical experience and the limited amount of evidence, the panel agreed that the basal plus 1 approach or twice-daily premixed insulin may provide equally effective and appropriate strategies for insulin intensification. Both regimens are logical, involve two injections, and both provide prandial cover at one or two meals, respectively. Both regimens may require titration over time with additional insulin injections.

An algorithm for insulin intensification based on the consensus of the panel is presented in Figure 1. The algorithm assumes that despite optimisation of the basal insulin dose, together with oral medication(s), a person has failed to achieve their pranidal (pre and post) blood glucose, and HbA_{1c} targets. In general, different combinations of oral agents may be used; however, metformin should be continued. In isolated cases, there may be a decision to switch between strategies.

Practical issues

When selecting the most appropriate intensification regimen, a range of factors, not just HbA_{1c}, should be taken into account. These include individual preference, convenience, education, flexibility, the type of injection device, side effects, carbohydrate distribution across meals and the cost to the patient. Most people with diabetes are comfortable with the fact that all intensification regimens require additional injections and understand the concept of insulin to 'cover' meals. Both regimens have advantages and disadvantages and a summary of factors to consider are listed in Table 1.

The transition from basal therapy to premixed insulin requires a change of device and, therefore, further education. However, people with a lifestyle characterised by highly regular routines may be suited to a regimen incorporating premixed insulin. This option provides good basal coverage but it should be remembered that premixed insulins, because of their fixed ratio of short- to long-acting insulin, do not provide the same degree of flexibility as a basal plus 1 option. They also require thorough mixing prior to injection to ensure consistent absorption. However, the premixed option does, of course, provide prandial cover for two meals.

With the basal plus 1 option, individuals have flexibility with the timing of both basal (e.g., morning or evening) and mealtime insulin injections, and can titrate the dose of both insulins independently of each other. Capable individuals can derive additional benefit by tailoring the

mealtime insulin dose to match the carbohydrate content of their meal. The basal plus 1 option also introduces people to the concept of meal time insulin and prepares them for a basal bolus strategy should further insulin intensification become necessary.

Conversely, people who select to follow the basal plus 1 regimen require the introduction of a new device, an extra prescription for the rapid acting portion of their insulin and additional education around meal time insulin doses according to their blood glucose measurements. If a different device is used for the rapid acting portion of insulin, education may be required to reduce the risk of confusing the type of insulin. The basal plus 1 regimen is, however, a conceptually simple extension of basal therapy.

In conclusion, the progressive nature of type 2 diabetes, reflective of the decline in pancreatic beta cell function, means that many people will eventually require insulin intensification to maintain glycaemic control. For clinicians faced with this situation, there are a number of strategies. The basal plus 1 regimen or a switch to premixed insulin are commonly used. The panel considered both strategies to offer comparable clinical efficacy with a range of advantages and disadvantages. Ultimately, the choice of regimen is the one that best meets the needs of the individual.

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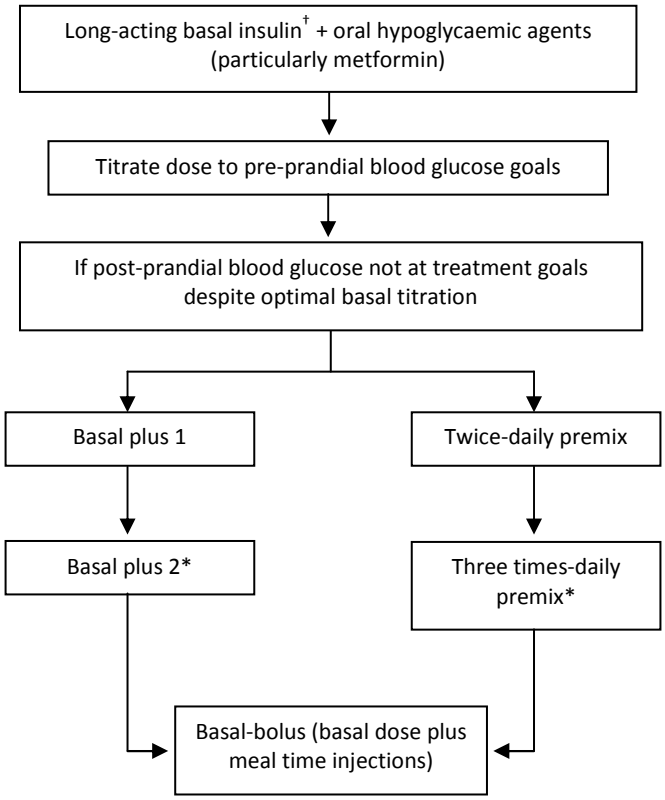
FIGURES AND TABLES

Figure 1: A practical algorithm for insulin intensification



Note: Multiple regimens may be used in clinical practice. The diagram refers to the most common approaches based on simplicity and the weight of evidence. At each stage ensure lifestyle factors are addressed with ongoing evaluation of individual needs.

†Basal insulin is the preferred option based on simplicity. Once-daily premixed insulin is an option for some people.

*Literature supports but not common in practice.

FBG – fasting blood glucose (patient-measured capillary glucose).

Table 1: Options for intensifying basal insulin with the addition of prandial cover

Regimen	Advantages	Disadvantages
Premixed insulin (bd)	• Prandial cover for 2 meals • Single prescription and device	• Change of device • Cannot separate basal and prandial titration • Requires thorough mixing
Basal plus 1	• Simple addition to basal therapy • Flexibility with timing of injections • Capacity to titrate basal and bolus separately • Natural progression from basal to basal-bolus strategy • No mixing required	• Requires extra prescription and extra device • Risk of confusing basal and bolus insulins if a similar injection device is used